

The background of the page is a faded, aerial photograph of a city. A prominent feature is a large, light-colored building with a central tower, situated on a riverbank. The river flows through the city, and other buildings and structures are visible in the distance. The overall color palette is muted, with a yellowish-green tint.

Tuesday November 7

10.00am – 12.30pm

Poster Session 3

Complex Traits Pages 159 - 184

Posters P-124 – P-165

Complex Traits

P-124 GENETIC VARIATION IN THE PROMOTER REGION OF POSITIONAL CANDIDATE GENES FOR OBESITY AND GROWTH

S Aksu¹, K Reichwald², U Renne³, G A Brockmann¹

¹ Institute for Animal Sciences, Humboldt-University, Berlin, Germany, ² The Clinic for Psychiatry and Psychotherapy of Children and Adolescence, University of Duisburg-Essen, Essen, Germany, ³ Research Institute for the Biology of Farm Animals, Dummerstorf, Germany

P-125 MULTIPLE QUANTITATIVE TRAIT LOCI MODIFY THE HEART FAILURE PHENOTYPE IN A MURINE MODEL OF CARDIOMYOPATHY

D A Marchuk, F.C. Wheeler, L Fernandez, K M Carlson, H A Rockman
Duke University Medical Center, Durham, North Carolina, United States

P-126 ROLE OF TRANSCORTIN IN ADIPOSE TISSUE: KNOCK OUT MICE ANALYSIS

E Richard, C Tridon, P Mormede, M P Moisan
INRA-Bordeaux University, Bordeaux, France

P-127 CHROMOSOME Y CONTRIBUTES TO FEATURES OF DILATED ECCENTRIC HYPERTROPHY IN MALE C57BL/6J MICE

B Llamas¹, D de Verteuil¹, A M Joseph-George², J MacDonald², C F Deschepper¹

¹ Institut de Recherche Clinique de Montréal, Montréal, QC, Canada, ² The Hospital for Sick Children, Toronto, ON, Canada

P-128 HOW DOES AN X-LINKED QTL INFLUENCING BODY WEIGHT IN MICE EXERT ITS EFFECT?

F Oliver

University of Edinburgh Institute of Evolutionary Biology, Edinburgh, United Kingdom

P-129 GENETIC ANALYSIS OF CRANIOFACIAL ARCHITECTURE OF THE MOUSE USING INTERSPECIFIC RECOMBINANT CONGENIC STRAINS (IRCS)

G Burgio¹, M Baylac², E Heyer³, J L Guénet¹, X Montagutelli¹

¹ Institut Pasteur, Paris, France, ² Muséum National d'Histoire Naturelle, Paris, France, ³ CNRS Laboratoire d'Anthropologie biologique du Musée de l'Homme, Paris, France

P-130 INFLUENCE OF GENETIC BACKGROUND IN A MOUSE MODEL OF ERYTHROPOIETIC PROTOPORPHYRIA; IDENTIFICATION OF A MAJOR MODIFIER LOCUS CONTROLLING ERYTHROCYTIC PROTOPORPHYRIN

M Abitbol¹, F Bernex¹, H Puy², H Jouault⁴, J C Deybach³, J L Guénet¹, X Montagutelli¹

¹ Institut Pasteur CNRS, Paris, France, ² Ecole Nationale Vétérinaire INRA, Maisons-Alfort, France, ³ INSERM Faculté Xavier Bichat, Colombes, France, ⁴ INSERM Université Paris 12, Créteil, France

P-131 GENETIC DISSECTION OF ANXIETY-MODULATING CAPABILITIES OF MG²⁺ IN MICE

M C Laarakker, D Schetters, S S Arndt, J R van Raai, F Ohl, H A van Lith

Utrecht University, Utrecht, Netherlands

P-132 GENETICAL AND PHYSIOLOGICAL ANALYSES IN THE FAT (F) AND LEAN (L) MICE PRODUCED BY LONG-TERM DIVERGENT SELECTION

M Simoncic¹, N M Morton², C J Kenyon², J R Seckl², I Stylianou³, L Buenger⁴, J Speakman⁵, P D Keightley², S. Horvat¹

¹ University of Ljubljana, Dept. Animal Science, Ljubljana, Slovenia, ² University of Edinburgh, Edinburgh, United Kingdom, ³ The Jackson Laboratory, Bar Harbor, United States, ⁴ Scottish Agricultural College, Bush Estate, United Kingdom, ⁵ Rowet Research Institute, Aberdeen, United Kingdom

P-133 FINE MAPPING OF THE *TMEVP3* LOCUS

M Mas, F Levillayer, F Levi-Acobas, M Szatanik, M Brahic, J F Bureau

Institut Pasteur, Paris, France

P-134 MAPPING QUANTITATIVE TRAIT LOCI FOR HEARING LOSS IN BLACK SWISS MICE

M Drayton, K Noben-Trauth

National Institute on Deafness and Other Communication Disorders, Rockville, MD, United States

- P-135 EFFECT OF THE GENETIC BACKGROUND ON THE PHENOTYPE OF THE FERROCHELATASE DEFICIENCY MUTATION OF THE MOUSE. LOOKING FOR MODIFYING GENES**
M Abitbol¹, F Bernex², H Puy³, M Rocancourt⁴, H Jouault⁵, JC Deybach³, J L Guenet¹, X Montagutelli¹
¹ Unité de Génétique des Mammifères and URA2579 CNRS, Institut Pasteur, Paris, France, ² UMR 955 INRA-ENVA de Génétique Moléculaire et Cellulaire and UP d'Histologie et d'Anatomie Pathologique, Maisons-Alfort, France, ³ Centre Français des Porphyries, INSERM U 409, Faculté X. Bichat, Hôpital Louis Mourier, Colombes, France, ⁴ Centre des Enseignements, Institut Pasteur, Paris, France, Paris, 75015, France, ⁵ INSERM U 492-Université Paris XII, Faculté de Médecine, Créteil, France
- P-136 FINE MAPPING OF QUANTITATIVE TRAIT LOCI (QTL) AND IDENTIFICATION OF CANDIDATE GENES ON MMU 8, 9 AND 11 FOR PRION DISEASE INCUBATION TIME IN MICE**
M O'Shea, R Mott, S Lloyd, J Collinge
¹ MRC Prion Unit, London, United Kingdom, ² Wellcome Trust Centre for Human Genetics, Oxford, United Kingdom
- P-137 THE COLLABORATIVE CROSS AT OAK RIDGE NATIONAL LABORATORY**
D K Johnson¹, E J Chesler¹, K F. Manly², E J Michaud¹, D R Miller¹
¹ Oak Ridge National Laboratory, Oak Ridge, TN, United States, ² University of Tennessee Health Sciences Center, Memphis, TN, United States
- P-138 QUANTITATIVE GENETIC VARIATION IN THE HEMATOPOIETIC STEM CELL COMPARTMENT DETERMINES HOMEOSTATIC STRESS RESPONSES IN THE HEMATOPOIETIC SYSTEM.**
 J Choi, L Gluchkova, R Kumar, H Kim, G Palmer, H W Snoeck
 Mount Sinai School of Medicine, New York, NY, United States
- P-139 TWO QTLs ON THE X CHROMOSOME INFLUENCE CORPUS CALLOSUM SIZE**
G Kusek¹, D Wahlsten², L Flaherty¹
¹ The Genomics Institute, Troy, New York, United States, ² Department of Biological Sciences and Great Lakes Institute, University of Windsor, Windsor, Ontario, Canada
- P-140 ANALYSIS OF QUANTITATIVE TRAIT LOCI THAT INFLUENCE DIVERSITY OF BEHAVIORAL TRAITS BETWEEN C57BL/6 AND MSM/MS**
A Nishi, A Takahashi, T Shiroishi, T Koide
 National Institute of Genetics, Mishima, Japan
- P-141 GENETIC ANALYSIS OF EMOTIONALITY IN B6-MSM CONSONIC MOUSE STRAINS**
A Takahashi, A Nishi, T Shiroishi, T Koide
 National Institute of Genetics, Mishima, Shizuoka, Japan
- P-142 A STUDY OF GENETIC FACTORS RESPONSIBLE FOR DIFFERENCE IN SPONTANEOUS LOCOMOTOR ACTIVITY BETWEEN INBRED STRAINS OF MOUSE**
J Umemori¹, A Nishi^{1,2}, T Shiroishi^{2,3}, T Koide^{1,2}
¹ Mouse Genomics Resource Laboratory, National Institute of Genetics, Japan. ² Department of Genetics, Sokendai, ³ Mammalian Genetics Laboratory, National Institute of Genetics
- P-143 A CONGENIC MOUSE STRAIN FOR QTL ON CHROMOSOME 2 AFFECTING GROWTH, FATNESS AND TESTIS SIZE**
A Ishikawa, E Kim, H Bolor, T Tanahashi, H Kodama, T Namikawa
 Nagoya University, Nagoya, Japan
- P-144 k-CASEIN DEFICIENT MOUSE FAILS TO LACTATE**
 P Chandra Shekhar, S Goel, D Selvi Rani, D Partha Sarathi, J L Alex, S Singh, S Kumar
 Centre for Cellular and Molecular Biology, Hyderabad (AP), India
- P-145 DETECTION OF QUANTITATIVE TRAIT LOCI AFFECTING SPERMATOGENESIS AND TESTIS WEIGHT FROM THE SMALL TESTIS MUTANT MOUSE**
H Bolor¹, N Wakasugi¹, W Zhao², A Ishikawa¹
¹ Nagoya University, Nagoya, Japan, ² Henan Agricultural University, Zhengzhou, China

- P-146 MAPPING OF AUTOSOMAL GENES RESPONSIBLE FOR HYBRID BREAKDOWN CAUSED BY X-CHROMOSOME SUBSTITUTION BETWEEN TWO MOUSE SUBSPECIES**
A Oka¹, A Mita¹, R Takahashi², T Aoto², Y Totsuka², M Ueda², N Yamatani¹, H Yamamoto¹, N Takagi³, K Moriawaki⁴, T Shiroishi¹
¹ The National Institute of Genetics, Mishima, Japan, ² The YS Institute, Inc., Utsunomiya, Japan, ³ Hokusei Gakuen University, Sapporo, Japan, ⁴ RIKEN BioResource Center, Tsukuba, Japan
- P-147 A NETWORK OF CIS- AND TRANS- ACTING GENES AFFECTING PROLIFERATIVE ACTIVITY OF MOUSE HEMATOPOIETIC STEM CELLS (HSC)**
L V Bystrykh, L M Kamminga, R van Os, A Ausema, E Weersing, B Dontje, P Terpstra, RC Jansen, G de Haan
UMCG RUG, Groningen, Netherlands
- P-148 DIFEOMORPHIC NEUROANATOMICAL ANALYSIS USING MRI OF A NEW DOMINANT ALLELE OF CACNA1A**
J G Sled¹, B J Nieman¹, S J Clapcote², G Xie², R M Henkelman¹, J C Roder²
¹Hospital for Sick Children, Toronto, ON, Canada, ² Samuel Lunenfeld Research Institute, Toronto, ON, Canada
- P-149 PHARMACOGENETICS OF PENTOBARBITAL - MEDIATED SEDATION**
CPD Tu, CC Hsu, B Akgul
¹ IBMS, Academia Sinica, Taipei, Taiwan, ² Pennsylvania State Univ., Univ. Park, PA, United States, ³ Izmir Institute of Technology, Urla, Izmir, Turkey
- P-150 INTER-SUBSPECIES CHROMOSOME SUBSTITUTION STRAINS OF MICE**
S Gregorova, R Storchova, P Divina, P Jansa, K Matejka, M Landikova, B Paigen, J Forejt
Institute of Molecular Genetics AS CR, Prague, Czech Republic
- P-151 A STATISTICAL MULTI-PROBE MODEL FOR ANALYZING CIS-AND TRANS-GENES IN GENETICAL GENOMICS EXPERIMENTS WITH SHORT-OLIGONUCLEOTIDE ARRAYS**
R Alberts, P Terpstra, L V Bystrykh, G de Haan, R C Jansen
Groningen University, Groningen, Netherlands
- P-152 MOUSE SNPS IN THE MGI DATABASE: USING LARGE-SCALE GENOMIC VARIATION TO IDENTIFY CANDIDATE GENES FOR COMPLEX TRAITS**
C J Bult, S Zhu, B Sinclair, D Qi, D Reed, D Bradt, K Frazer, R Baldarelli, S Cousins, J Winslow, J Beal, J Kadin, J Richardson, L Corbani
The Jackson Laboratory, Bar Harbor, Maine, United States
- P-153 GENE EXPRESSION DIFFERENCES CORRELATE WITH SPATIAL LEARNING IN MIDDLE AGED MICE ON ATHEROGENIC DIET**
AN Desai, BS Beyer, KP Collins, AF Eisener, TA Gray, BJ Herron, GK Kusek, A Messer, RL Pietropaolo, J L Phoenix, MP Ryan, AB Smith, DJ Symula, VJ Bolivar, L Flaherty
¹ The Genomics Institute, Wadsworth Center, New York State Department of Health, Troy, NY, United States, ² Department of Biomedical Sciences, University at Albany, Albany, NY, United States
- P-154 IDENTIFICATION OF A QUANTITATIVE TRAIT LOCUS AFFECTING HIPPOCAMPUS-RELATED BEHAVIOR IN THE INTERLEUKIN-7 RECEPTOR KNOCKOUT MOUSE**
A F Eisener, V J Bolivar, R L Pietropaolo, L Flaherty
The Genomics Institute, Wadsworth Center, New York State Department of Health, Department of Biomedical Sciences, University at Albany, Troy, NY, United States
- P-155 CHROMOSOME SUBSTITUTION STRAINS HELP TO DISSECT LARGE QTL INTERVALS FOUND PREVIOUSLY IN F₂ CROSSES, AND REVEAL SIGNIFICANT QTL ON CHROMOSOMES THAT WERE NOT PREVIOUSLY DETECTED**
I M Stylianou¹, K Russell², P Magnani¹, B J Paigen¹
¹ The Jackson Laboratory, Bar Harbor, Maine, United States, ² University of Missouri-Rolla, Rolla, MO, United States

- P-156 GENOME-WIDE HAPLOTYPE ASSOCIATION STUDIES TO LOCATE QTL AND QTL GENES**
 I Stylianou¹, K Russell², P Magnani¹, B Paigen¹
¹ The Jackson Laboratory, Bar Harbor, ME, United States, ² University of Missouri-Rolla, Rolla, MO, United States
- P-157 GENETIC MODIFIERS OF NPC2 DEFICIENCY IN MICE**
D Symula, K Collins, M Darrah
 Wadsworth Center, Albany, NY, United States
- P-158 TESTICULAR GERM CELL TUMOR DEVELOPMENT IN THE 129.MOLF-CHR 19 CONSONIC MOUSE STRAIN**
A Matin, R Zhu, C Bhattacharya
 UT MD Anderson Cancer Center, Houston, Texas, United States
- P-159 OLIGOGENIZATION OF MULTIGENIC TRAITS: USING A CROSS BETWEEN CONGENIC AND INBRED STRAINS TO REDUCE COMPLEXITY OF QUANTITATIVE TRAITS**
AA Bachmanov, X Li, N Bosak, M L Theodorides, M G Tordoff, G K Beauchamp, D R Reed
 Monell Chemical Senses Center, Philadelphia, PA, United States
- P-160 MAPPING GENE(S) RELATED TO NOVELTY-INDUCED BEHAVIORS IN INBRED STRAINS OF MICE**
H Shin, S Chae, D Kim, J Lee
 Korea Institute of Science and Technology, Seoul, Korea, South
- P-161 MOUSE KOALA INVERSION MUTATION DISRUPTED NO GENE, BUT EXPRESSION OF *HOXC* GENES WAS ALTERED, AND THE EAR-HAIR UNDERWENT HOMEOTIC TRANSFORMATION**
Y You¹, J Sundberg², A Awgulewitsch³, S Mentzer¹, D Carpenter¹, D Johnson¹, E Rinchik¹
¹ Oak Ridge National Laboratory, Oak Ridge, TN, United States, ² The Jackson Laboratory, Bar Harbor, ME, United States, ³ Medical University of South Carolina, Charleston, SC., United States
- P-162 IDENTIFYING NOVEL GENES REGULATING ATHEROSCLEROSIS AND PLASMA LIPID CONCENTRATIONS THROUGH MOUSE-HUMAN COMPARATIVE GENETICS**
 X Wang, J Rollins, B Paigen
 The Jackson Laboratory, Bar Harbor, ME, United States
- P-163 A GRAPH THEORETICAL APPROACH TO SYSTEMS GENETIC ANALYSIS OF GENE TRANSCRIPTION AND COMPLEX PHENOTYPES ACROSS BIOLOGICAL SCALE**
E J. Chesler¹, J A Scharff², S M Pitts¹, L Lu¹, J Wang¹, K F Manly¹, M A Langston², R W Williams¹
¹Center for Genomics & Bioinformatics, University of Tennessee Health Science Center, Memphis, TN, United States, ² Department of Computer Science, University of Tennessee, Knoxville, TN, United States
- P-164 THE ORIGINS AND USES OF MOUSE OUTBRED STOCKS**
 R Chia¹, F Achilli¹, M F W Festing², E M C Fisher¹
¹Department of Neurodegenerative Disease, Institute of Neurology, London, UK; ²c/o MRC Toxicology Unit, Hodgkin Building, University of Leicester, Leicester, UK
- P-165 STUDENT ORAL ABSTRACT S-16**
GENETIC DISSECTION OF THE MOUSE RESPONSE TO SALMONELLA TYPHIMURIUM USING RECOMBINANT CONGENIC STRAINS
MF Roy¹, JC Loredano-Osti¹, C Bédard², K Morgan¹, P Gros¹, D Malo¹
¹ McGill University, Montreal, Qc, Canada, ² Université de Montréal, St-Hyacinthe, Qc, Canada

P-124**GENETIC VARIATION IN THE PROMOTER REGION OF POSITIONAL CANDIDATE GENES FOR OBESITY AND GROWTH**

S Aksu¹, K Reichwald², U Renne³, G A Brockmann¹

¹ Institute for Animal Sciences, Humboldt-University, Berlin, Germany, ² The Clinic for Psychiatry and Psychotherapy of Children and Adolescence, University of Duisburg-Essen, Essen, Germany, ³ Research Institute for the Biology of Farm Animals, Dummerstorf, Germany

In this study, we used the high body weight selected mouse line DU6 and its inbred derivative DU6i as animal models for obesity. High body weight selected DU6 mice are twice as heavy and three times as fat as unselected DUK and DBA/2 control mice. Recently, we have determined several quantitative trait loci (QTL) that are responsible for differences in obesity and growth between these lines. Using Microarray GeneChip and Real-Time PCR analyses, 10 positional candidate genes located on previously identified QTL regions were differently expressed between selected and control mouse lines ($p < 0.05$). To identify DNA sequence variations which might be a cause for the different gene expression, we sequenced 5' and 3'-flanking, putatively regulatory regions of the positional candidate genes in selected and control lines. We identified several single nucleotide polymorphisms (SNPs) some of which are located in putative transcription factor binding sites. We postulate that these SNPs underlie the determined QTL effects.

P-125**MULTIPLE QUANTITATIVE TRAIT LOCI MODIFY THE HEART FAILURE PHENOTYPE IN A MURINE MODEL OF CARDIOMYOPATHY**

D A Marchuk, F C Wheeler, L Fernandez, K M Carlson, H A Rockman
Duke University Medical Center, Durham, North Carolina, United States

The progression from heart disease to heart failure is a complex process, involving both environmental and genetic factors. Unfortunately, elucidating the genetic components contributing to heart failure has been difficult, due largely to the heterogeneity of human populations. We have undertaken an unbiased genetic mapping approach in a genetically-sensitized mouse strain to identify novel genes that contribute to the progression of heart disease. In a well-studied transgenic mouse model of cardiomyopathy, we discovered dramatic strain-specific differences in both disease progression and survival. Using a QTL mapping approach in multiple crosses, we have identified seven distinct genetic loci, *Hrtfm1-7* (Heart failure modifier), that modify the heart failure phenotype. Significantly, the phenotypic effects of these modifier loci recapitulate the complexities of human heart disease, with some loci affecting both heart function and survival, but with others separately influencing these two phenotypes. Gene identification in the mouse has employed congenic strains for each locus, recombinant progeny testing to assist fine-mapping, DNA sequence analyses to identify sequence variants, and prioritization of candidate genes using mRNA expression analysis. In one case, we mapped the identical QTL in two different crosses between strains of dramatically different phenotypic outcomes. This allowed us to use ancestral haplotypes to narrow the candidate gene interval for this locus. Intriguingly, one of the few genes that exhibit strain-specific differences in heart expression maps within the shared haplotype region at this locus. Further investigation of this candidate gene shows that a cryptic splice site is activated in a number of inbred strains which exhibit low expression of the gene, implicating aberrant splicing and nonsense mediated decay of the resulting message as a likely mechanism for reduced expression at this locus. Identification and characterization of this and the other genetic modifiers will increase our understanding of the molecular mechanisms underlying the development and progression of heart disease, and provide novel targets for translation to human heart disease.

P-126**ROLE OF TRANSCORTIN IN ADIPOSE TISSUE: KNOCK OUT MICE ANALYSIS**

E Richard, C Tridon, P Mormede, M P Moisan
INRA-Bordeaux University, Bordeaux, France

Transcortin is a strong functional candidate of a QTL associated with cortisol levels and fat deposition that we have detected in a previous study.

CBG acts as a carrier protein that regulates glucocorticoids bioavailability in playing a role in hormone sequestration but also in delivery to tissue. It could also play a local role in the lipogenic action of glucocorticoids in adipose tissue.

To evaluate further the role of transcortin in obesity susceptibility, we investigate its presence in various adipose tissues in performing a duplex PCR. Transcortin mRNA expression have been detected in all fat tissues. A higher transcortin expression was found in omental fat tissue by quantitative real time PCR. Thus, an adipose-tissue knock out of *transcortin* gene should provide interesting clues on the role of transcortin in this tissue.

To take into account the role of transcortin both in plasma and in peripheral tissues, we are producing a line of mice deleted totally for *transcortin* gene expression and another one deleted only in the adipose tissue and conditionally, using Cre-Lox system. Mice bearing exon 2 of *transcortin* gene flanked by loxP sequences have been constructed. These mice are crossed in one hand with CMV-Cre mice to create a knock-out line and in the other hand with aP2-ER^{T2}-Cre (adipocyte fatty acid binding protein) mice to create the other line.

On these animals, we will study the influence of ablation of *transcortin* gene expression on hypothalamo-pituitary-adrenal axis and on development of obesity.

P-127**CHROMOSOME Y CONTRIBUTES TO FEATURES OF DILATED ECCENTRIC HYPERTROPHY IN MALE C57BL/6J MICE**B Llamas¹, D de Verteuil¹, AM Joseph-George², J MacDonald², C F Deschepper¹¹ Institut de Recherche Clinique de Montréal, Montréal, QC, Canada, ² The Hospital for Sick Children, Toronto, ON, Canada

The hearts of male C57Bl/6J mice display features of dilated eccentric hypertrophy when compared to that of male A/J mice. Likewise, we have verified that the length of isolated adult cardiomyocytes (CMs), a variable that correlates closely with the size of the left ventricular cavity, was longer in C57Bl/6J male mice than in their A/J counterparts (see Table). In males from the B6AF1 cross (resulting from the cross between a female C57Bl/6J and a male A/J mouse), the length of CMs was $132.9 \pm 0.8 \mu\text{m}$, similar to that of CMs from male A/J mice. In contrast, in males from the reciprocal AB6F1 cross, the length of CMs was $144.7 \pm 1.0 \mu\text{m}$, and thus significantly higher than that of CMs from the B6AF1 cross. To test whether the chromosome Y (MMUY) from C57Bl/6J contributes to these various differences, we compared the cardiac phenotypes of consomic C57Bl/6J-Chr Y<A>/NaJ mice (where MMUY from A/J has been introgressed into the C57Bl/6 genetic background) to that of the parental strains. In the consomic mice, the values of CM length, relative wall thickness and mitral flow were intermediate between that of C57Bl/6 and A/J mice (see table), thus confirming the contribution of MMUY from C57Bl/6 to the morphology of the left ventricle and the CMs that comprise it.

Variable	C57Bl/6	C57Bl/6J-Chr Y<A>/NaJ	A/J
CM length (μm)	160.1 ± 0.8	141.7 ± 0.5	133.2 ± 1.0
Relative wall thickness (ratio)	0.577 ± 0.031	0.743 ± 0.039	0.706 ± 0.044
Mitral velocity trace (cm)	7.62 ± 0.39	6.35 ± 0.24	5.65 ± 0.22

In the May 2004 chromosomal assembly, a total of 24 genes have been mapped to MMUY, including one cluster of 3 genes apparently duplicated from MMU5, and another one of 6 genes duplicated from MMU15. However, the assignment of these 2 clusters to MMUY is likely to result from an assembly artefact, because chromosomal localisation of corresponding genes by FISH revealed only autosomal signals. Out of 15 remaining genes, 5 of them were found to be expressed in the hearts of adult C57Bl/6 and A/J mice in a male-specific fashion. Additional experiments are underway to test whether these genes are expressed at different levels in the hearts of C57Bl/6 and A/J male mice during development, and thus maybe provide a molecular clue for the phenotypic cardiac differences between the two strains. Of note, our data may also partly explain why certain cardiac transgenes display sex-specific phenotypes when expressed into the C57Bl/6J background.

P-128**HOW DOES AN X-LINKED QTL INFLUENCING BODY WEIGHT IN MICE EXERT ITS EFFECT?**

F Oliver

University of Edinburgh Institute of Evolutionary Biology, Edinburgh, United Kingdom

An X-linked QTL responsible for ~20% increase in body weight in mice has recently been found to be allelic with the Glypican 3 gene (GPC3), with differences found in the level of GPC3 mRNA expression in liver and kidney between an inbred low line (Low line) and a congenic for a high line segment of the X Chromosome containing the QTL region (High line). Loss of function mutations in GPC3 are associated with overgrowth in humans and mice.

GPC3 deficient mice are known to show morphological differences in kidney, spleen and placenta. Recent studies of our High and Low lines have shown no obvious histological differences. A previous study has looked at differences in weight of various internal organs and found significant increases in the High line. This study will look for differences with regard to cell counts and morphology in kidney and liver. We will investigate whether our observed increase in body weight is maintained in increased weight of organs and use histological methods to investigate whether any weight increases have corresponding changes in cell size in these organs in an attempt to discover whether the mechanism of our QTL involves an increase in cell size or cell number.

Muscle fibre numbers, blood supply and overall size are known to be affected by selection based on body size. We therefore also intend to investigate whether our mouse lines show any significant differences in quadriceps muscle composition by using staining techniques to distinguish different muscle fibre types and calculate capillary distribution.

P-129**GENETIC ANALYSIS OF CRANIOFACIAL ARCHITECTURE OF THE MOUSE USING INTERSPECIFIC RECOMBINANT CONGENIC STRAINS (IRCS)**G Burgio¹, M Baylac², E Heyer³, J L Guénet¹, X Montagutelli¹¹ Institut Pasteur, Paris, France, ² Muséum National d'Histoire Naturelle, Paris, France, ³ CNRS Laboratoire d'Anthropologie biologique du Musée de l'Homme, Paris, France

Genetic determinism of cranial morphology is complex and largely unknown in the human. An animal model such as the mouse may be very useful in identifying genes which play a key-role in skull morphogenesis. Interspecific recombinant congenic strains (IRCS) are inbred strains produced from crosses between the laboratory inbred strain C57BL/6 and mice of the distant species *Mus spretus* (inbred strain SEG/Pas). Each of the 55 IRCS carries a small number of chromosomal segments of *Mus spretus* origin (with an average size of less than 10 cM) in an otherwise C57BL/6 background. On average 1.8%, of the genome of these strains come from SEG/Pas. Fifteen IRCS have been phenotyped for morphological and biometrical parameters and compared to C57BL/6. Statistically significant differences in the frequency of morphological features and in bones conformation have been found, using either procruste or outline analysis. Our data show that these strains show specific cranio-facial conformations. For example, SEG/Pas and C57BL/6 mice show significant differences in the shape of nasal bone, and IRCS strain 66H has an intermediate phenotype, as revealed by outline and principal component analysis. To identify which of the genomic regions that 66H has inherited from SEG/Pas are responsible for this phenotype, an F2 cross between 66H and C57BL/6 was produced. ANOVA revealed the presence of two QTLs on Chr 1 (between *D1Mit305* and *D1Mit137*, 8 cM) and on Chr 18 (between *D18Mit23* and *D18Mit123*, 10 cM), which show additive effects. The identification of the causative genes is under progress and will take advantage of the simple genetic architecture of IRCS.

P-130**INFLUENCE OF GENETIC BACKGROUND IN A MOUSE MODEL OF ERYTHROPOIETIC PROTOPORPHYRIA; IDENTIFICATION OF A MAJOR MODIFIER LOCUS CONTROLLING ERYTHROCYTIC PROTOPORPHYRIN**M Abitbol¹, F Bernex¹, H Puy², H Jouault⁴, J C Deybach³, J L Guénet¹, X Montagutelli¹¹ Institut Pasteur CNRS, Paris, France, ² Ecole Nationale Vétérinaire INRA, Maisons-Alfort, France, ³ INSERM Faculté Xavier Bichat, Colombes, France, ⁴ INSERM Université Paris 12, Créteil, France

Erythropoietic protoporphyria (EPP) is an inherited disorder of heme biosynthesis caused by partial ferrochelatase deficiency, resulting in protoporphyrin overproduction by erythrocytes. In humans, it is responsible for painful skin photosensitivity and occasionally liver failure due to the accumulation of protoporphyrin in the liver. The ferrochelatase deficiency mouse mutation is the best animal model available for human EPP. The original description, based on mice with a BALB/cByJCrI genetic background, reported a disease resembling the severe form of the human disease with anemia, jaundice and liver failure. We investigated the effect of the genetic background on the severity of the phenotype using congenic strains. Compared with BALB/cByJCrI, C57BL/6JCrI mice developed moderate but increasing anemia, and intense liver accumulation of protoporphyrin with severe hepatocytes damage and loss. However, bile excretory function was not affected and bilirubin remained low. Despite highest protoporphyrin concentration in erythrocytes, SJL/JOrIcrI homozygotes had mild anemia, and few liver deposits of protoporphyrin. Discriminant analysis using six hematological and biochemical parameters showed that homozygotes of the three genetic backgrounds could be clustered in three well-separated groups.

Three F2 intercrosses were produced between all pairs of congenic strains in order to identify modifier loci. Fifteen quantitative traits were measured on approx. 200 mice for each cross. Several QTLs were identified with significant linkage. Most interestingly, we identified a very strong QTL (LOD score >30, >60% variance explained) which controls the accumulation of protoporphyrin in erythrocytes. Future work will aim at refining the position and eventually identify the major QTLs identified in the F2 crosses.

P-131**GENETIC DISSECTION OF ANXIETY-MODULATING CAPABILITIES OF Mg^{2+} IN MICE**

M C Laarakker, D Schettters, S S Arndt, J R van Raai, F Ohl, H A van Lith
Utrecht University, Utrecht, Netherlands

There is evidence that Mg^{2+} deficiency may causally be involved in stress-responses and modulation of emotionality. It has as well been hypothesised that genetically based low blood Mg^{2+} levels may account for stress susceptibility. We aim at evaluating whether *i)* differences in anxiety-related behaviour in inbred mouse strains correspond to plasma Mg^{2+} concentration and *ii)* whether systemic treatment with Mg^{2+} abolishes possibly corresponding strain differences. The long-term goal of our project is to evaluate the genetic background for anxiety-modulating capabilities of Mg^{2+} in mice. Therefore, we have chosen to investigate the A/J and C57BL/6J strains which are the parental strains of the commercially available set of chromosome substitution strains (CSSs) that can be used for further genetic analysis. In the here reported experiment, BALB/c mice are used as an additional control group since this strain has extensively been reported to be characterised by high innate anxiety. All three inbred strains are behaviourally tested in the modified hole board, allowing for the parallel evaluation of a variety of motivational systems potentially involved in emotionality. One week after initial testing, the animals are re-tested after having received either vehicle or magnesiumsulphate. Subsequently to behavioural testing blood will be sampled (analysis of plasma Mg^{2+} concentrations as well as stress hormone responses). Our first pilot studies have shown that the CSS-parental strains differ in a variety of behavioural parameters, including anxiety-related measures, which corresponds with differences in plasma Mg^{2+} levels. These results emphasise the hypothesised and possibly causal association between magnesium status and emotionality.

P-132**GENETICAL AND PHYSIOLOGICAL ANALYSES IN THE FAT (F) AND LEAN (L) MICE PRODUCED BY LONG-TERM DIVERGENT SELECTION**

M Simoncic¹, N M Morton², C J Kenyon², J R Seckl², I Stylianou³, L Buenger⁴, J Speakman⁵, P D Keightley²,
S Horvat¹

¹ University of Ljubljana, Dept. Animal Science, Ljubljana, Slovenia, ² University of Edinburgh, Edinburgh, United Kingdom, ³ The Jackson Laboratory, Bar Harbor, United States, ⁴ Scottish Agricultural College, Bush Estate, United Kingdom, ⁵ Rowet Research Institute, Aberdeen, United Kingdom

A polygenic model differing five fold in fat percentage (fat%) was developed at the University of Edinburgh by long-term divergent selection in mice (60 generations) for high (Fat, F line) or low (Lean, L line) fat%. At least 4 QTLs on chromosomes 2, 12, 15 and X have been detected and the Chr 15 QTL was further mapped using congenic strains to two or more linked loci. Microarray analysis demonstrated differential expression of cholesterol and glycolysis pathway genes. Currently, interval specific congenic strains and single nucleotide polymorphisms markers (SNP) are being used for high-resolution mapping of the Chr 15 QTL. Recent physiological studies aim at better defining phenotypic differences between the F, L and congenic lines. The F mice were shown to have a complete metabolic syndrome with insulin resistance, hypertension and fatty liver associated with their obesity. In contrast to monogenic obesity models, F mice have deficiency of adipose tissue 11 β -HSD-1 and plasma glucocorticoids but higher liver glucocorticoid action making these mice an interesting model of human disease. Previous energy budget analysis indicated that physical activity and thermoregulation could explain a large proportion of the phenotypic difference between the lines. A preliminary experiment using running wheels confirmed that physical activity is higher in the L line. Combined genetic and physiological approaches should lead eventually to identification of mutations and pathways that regulate predisposition or resistance to obesity and metabolic syndrome in the F or L lines, respectively.

P-133**FINE MAPPING OF THE *TMEVP3* LOCUS**

M Mas, F Levillayer, F Levi-Acobas, M Szatanik, M Brahic, J F Bureau
Institut Pasteur, Paris, France

The demyelinating disease induced by the persistent infection of Theiler's virus in mouse spinal cord is studied as a model for Multiple Sclerosis. Susceptibility to infection amongst mouse strains depends mainly on the ability of their immune system to clear the virus. By studying crosses between the SJL/J and the B10.S strains, two susceptibility loci, named *Tmevp2* and *Tmevp3*, were located on chromosome 10. At the telomeric part of the *Tmevp3* interval, a cluster of cytokines containing at least 3 genes: *Tmevpg1*, *Ifng*, and *Il-Tif/IL22* is a candidate region since major susceptibility loci between the two parental strains are expressed in the immune system.

We test this hypothesis by haplotyping this cluster in 15 strains: 11 laboratory strains with known susceptibility to the Theiler's persistence and 4 wild-type derived strains. Haplotypes of laboratory strains are divided in at least two groups. The first group contains the SJL/J and the NZB strains and the second group the 9 other ones. The good correlation between these haplotypes and susceptibility to Theiler's persistence strongly suggests that the *Tmevp3* locus is located in this cluster.

No polymorphism in the coding sequence of the *Ifng* and *Il-Tif/IL22* genes explains the effect of *Tmevp3*. The expression of these genes were significantly different between parental and congenic mice, ex vivo in CD4⁺ and CD8⁺ splenocytes, and in vivo during the infection by Theiler's virus. All these differences are explained by the *Tmevp3* haplotype. These data suggest that the *Tmevp3* controls difference of expression of *Ifng* and *IL22*.

P-134**MAPPING QUANTITATIVE TRAIT LOCI FOR HEARING LOSS IN BLACK SWISS MICE**

M Drayton, K Noben-Trauth

National Institute on Deafness and Other Communication Disorders, Rockville, MD, United States

In common inbred strains, hearing loss is a highly prevalent, quantitative trait, which is to a large extent controlled by the *Cdh23*^{753A} variant and alleles of heterogeneous strain-specific loci. The goal of this study was to determine the genetic basis of hearing loss in non-inbred strains. We show that outbred mice of Swiss Webster, CF-1, NIH Swiss, ICR, and Black Swiss strains exhibited hearing profiles characteristic of progressive sensorineural hearing loss. BUB/BnJ and A/J mice complement the Black Swiss phenotype, and NIH Swiss and CF-1 show partial allelism, primarily at the higher frequency stimulus. By quantitative trait loci (QTL) mapping of backcross and intercross progeny, we identify three QTLs underlying hearing loss in Black Swiss: a main QTL resides on chromosome (chr) 10 (*ahl5*) and two minor QTLs localize to chr 13 (*ahl6*) and chr 18 (*ahl7*). N2 progeny homozygous at the three QTL intervals replicate the hearing loss in the parental Black Swiss strain. Cadherin 23 (*Cdh23*) and protocadherin 15 (*Pcdh15*), mapping within the 95% confidence interval of *ahl5*, bear nucleotide polymorphisms in coding exons, which appear to be unrelated to the hearing phenotype. Cluster analyses-based genealogical comparisons show that Black Swiss strain is distinct from common inbred strains and related to the *Mus musculus domesticus* PERC/Ei strain. The data provide the framework for identifying the *ahl5* QTL and to elucidate the genetic architecture of hearing loss in outbred strains.

P-135**EFFECT OF THE GENETIC BACKGROUND ON THE PHENOTYPE OF THE FERROCHELATASE DEFICIENCY MUTATION OF THE MOUSE. LOOKING FOR MODIFYING GENES**

M Abitbol¹, F Bernex², H Puy³, M Rocancourt⁴, H Jouault⁵, J C Deybach³, J L Guenet¹, X Montagutelli¹

¹ Unité de Génétique des Mammifères and URA2579 CNRS, Institut Pasteur, Paris, 75015, France, ² UMR 955 INRA-ENVA de Génétique Moléculaire et Cellulaire and UP d'Histologie et d'Anatomie Pathologique., Maisons-Alfort, 94700, France, ³ Centre Français des Porphyrines, INSERM U 409, Faculté X. Bichat, Hôpital Louis Mourier, Colombes, France, Colombes, 92700, France, ⁴ Centre des Enseignements, Institut Pasteur, Paris, France, Paris, 75015, France, ⁵ INSERM U 492-Université Paris XII, Faculté de Médecine, Créteil, France, Créteil, 94000, France

The ferrochelatase deficiency mutation of the mouse, which arose in a genetic background very close from the BALB/cJ inbred strain, after mutagenic treatment with ethylnitrosourea, is a good model for human erythropoietic protoporphyria. Mutant mice exhibit photo-sensibility, icterus, enlarged abdomen (due to hepato and splenomegaly) and anaemia. While transferring the mutation into several inbred backgrounds (BALB/cJ, C57BL/6J, SJL/J) it became rapidly obvious that the severity of the phenotype was strongly modified. We established a series of congenic strains by introducing the ferrochelatase deficiency mutation into C57BL/6J and SJL/J genetic backgrounds and analyzed the phenotype of mutant mice of various classes of age, to characterize the peculiarities associated with each strain. We observed clinical, haematological, biochemical and histological differences among mice from the three congenic strains.

From this model of erythropoietic protoporphyria studied in three backgrounds we have developed three models of protoporphyria which allow to better reflect the variety of phenotypes observed in man. These three congenic strains provide strong evidence for independent genetic control of bone-marrow contribution of protoporphyrin overproduction to the development of liver disease, and of biliary protoporphyrin excretion.

These models have help to undertake a genetic study with the aim of identifying, by a QTL approach, genomic regions controlling these differences. We have yet identified a very strong QTL in the F2(BALB/cxSJL/J) and F2(SJL/JxC57BL/6J) crosses which control protoporphyrin accumulation in red blood cells and many other QTLs controlling various parameters in the three F2 crosses.

These three congenic strains provide a tool to investigate the physiological mechanisms involved in these and other yet unraveled phenotypic differences, and to identify modifying genes.

P-136**FINE MAPPING OF QUANTITATIVE TRAIT LOCI (QTL) AND IDENTIFICATION OF CANDIDATE GENES ON MMU 8, 9 AND 11 FOR PRION DISEASE INCUBATION TIME IN MICE**

M O'Shea, R Mott, S Lloyd, J Collinge

¹ MRC Prion Unit, London, United Kingdom, ² Wellcome Trust Centre for Human Genetics, Oxford, United Kingdom

Prion diseases are progressive neurodegenerative diseases which show characteristic prolonged incubation periods. Polymorphisms in the prion protein gene (*Prnp*) are known to influence incubation time but additional genetic loci have been identified by quantitative trait locus (QTL) mapping studies in mice. Genome-wide screening approaches using two-way crosses have identified broad regions of linkage with large confidence intervals on several mouse chromosomes including Mmu 8, 9 and 11. In order to reduce and fine map these regions, a genetically diverse heterogenous stock (HS) of mice, produced from randomly breeding eight inbred lines over 37 generations, has been utilized. The HS cross provides a powerful tool for fine mapping at 1cM intervals. HAPPY linkage analysis of the HS mice identified small (1-2cM), highly significant regions of linkage on chromosomes 8, 9 and 11. The promoter, regulatory regions and entire mRNA transcript of candidate genes within these regions are being sequenced to identify polymorphisms between the parental strains of the mice. This variation may be indicative of genetic differences that influence prion disease incubation time. Haplotype maps are being constructed to identify patterns of polymorphism distribution and HAPPY linkage analysis software will be used to determine if observed polymorphisms correlate with the strain effects identified in the HS cross. Candidate functional polymorphisms identified by HAPPY will be further investigated and used for additional mapping in the original mouse crosses. The identification of modifier genes influencing susceptibility to prion diseases will allow the realistic assessment of possible at-risk groups within populations exposed to prions, provide further insights into the pathogenesis of prion disease and identify ligands and pathways for the design of rational therapeutics.

P-137**THE COLLABORATIVE CROSS AT OAK RIDGE NATIONAL LABORATORY**D K Johnson¹, E J Chesler¹, K F Manly², E J Michaud¹, D R. Miller¹¹ Oak Ridge National Laboratory, Oak Ridge, TN, United States, ² University of Tennessee Health Sciences Center, Memphis, TN, United States

Oak Ridge National Laboratory (ORNL) will provide a home for the generation of the Complex Trait Consortium's 8-way Collaborative Cross. ORNL's Mouse Genetics Research Facility is a new, specific-pathogen free barrier vivarium designated as an official Department of Energy (DOE) User Facility. This facility can provide both the housing capacity and the mouse-genetics expertise to produce up to 1000 recombinant inbred strains with joint funding from the DOE and other federal and non-federal sponsors.

Our new vivarium can house 80,000 mice in ventilated racks with automated watering, and 24-hour electronic monitoring of environmental parameters. ORNL supplies a professional technical staff with decades of experience in complex genetic crosses, and AALAS-certified animal care staff. Inside the barrier are laboratory procedure rooms and soundproofed behavior-test rooms, and outside are standard molecular biology laboratories that can be shared by guest investigators for phenotyping. Additional reference populations are housed on-site for genetic analyses.

A breeding protocol has been implemented for maximizing the genetic diversity of the RI strain set using the minimum number of cages, and software for husbandry has been developed. By November, 400 "funnels" will be in mating, with the remaining 1280 to be initiated as additional F₁ progenitors arrive at ORNL.

As we progress beyond the one-gene-at-a-time era toward integrative systems genetic analysis, the ORNL Mouse Genetics Research Facility offers a quality environment for and a long-term commitment to the generation of unique mouse resources that can be phenotyped here or supplied for phenotyping to any approved mouse facility.

P-138**QUANTITATIVE GENETIC VARIATION IN THE HEMATOPOIETIC STEM CELL COMPARTMENT DETERMINES HOMEOSTATIC STRESS RESPONSES IN THE HEMATOPOIETIC SYSTEM**J Choi, L Gluchkova, R Kumar, H Kim, G Palmer, H W Snoeck

Mount Sinai School of Medicine, New York, NY, United States

The hematopoietic stem cell (HSC) compartment in the mouse shows extensive quantitative genetic variation. The goal of our studies is to investigate its organismal consequences, and to identify QTL involved. This work led to the identification of a network that regulates HSC in conditions of hematopoietic stress, and is subject to quantitative genetic variation. This network involves transforming growth factor-beta2 (TGF- β 2), a positive regulator of HSC function in conditions of hematopoietic stress; a serum factor that affects TGF- β 2 signaling and is regulated by stress; and an alternative splice variant of TGF- β 2 that is induced by stress, is regulated by TGF- β 2 signaling, and antagonizes some, but not all the effects of TGF- β 2 on HSC. Finally, both TGF- β 2 and its splice variant regulate signaling through Tie-2, a critical receptor for HSC. These components form a network, wherein several nodes are regulated by stress, and whose output is the rate of stem cell cycling. Disturbing this network, by changing parameters at the nodes using appropriate knockout and congenic mice, had no detectable effect on steady-state hematopoiesis, but profoundly affected hematopoietic homeostasis after stress. From an evolutionary point of view, the maintenance, likely by balancing selection, of quantitative variation in this network may allow homeostatic adaptation of the hematopoietic system to varying environments at the population level. Individuals with low levels of HSC cycling would be protected from agents toxic for HSC, while individuals with high levels of HSC cycling are capable of rapid recovery after depletion of mature cells.

P-139**TWO QTLs ON THE X CHROMOSOME INFLUENCE CORPUS CALLOSUM SIZE**G Kusek¹, D Wahlsten², L Flaherty¹¹ The Genomics Institute, Troy, New York, United States, ² Department of Biological Sciences and Great Lakes Institute, University of Windsor, Windsor, Ontario, Canada

The corpus callosum is the largest fiber tract in the brain that connects the left and right cerebral hemispheres. Corpus callosum size is a complex quantitative trait showing a continuous range of values and is influenced by interactions between multiple genes and environmental effects. Reciprocal crosses between inbred mouse strains BTBR *T/+ tf/tf* (BTBR), lacking a corpus callosum, and BALB/cByJ (BALB), having a corpus callosum, indicate the presence of an X-linked gene(s) affecting corpus callosum size. Analysis of variance (ANOVA) showed significant differences in the midsagittal corpus callosum area (corrected for brain weight) between (BTBR x BALB)F1 and (BALB x BTBR)F1 male mice ($p < .0001$), while there was no difference in midsagittal corpus callosum area between reciprocal females ($p = .9885$). Specifically, the X chromosome derived from BTBR possessed a dominant allele(s) resulting in a decrease in the mean midsagittal area of the corpus callosum. Genotyping 420 backcross male progeny identified 2 regions peaking at 65Mb and 131Mb on the X chromosome which influenced corpus callosum size. Microarray analyses are now being performed to determine gene expression differences that are influenced by the X chromosome. In addition, candidate genes within this region are currently being examined by sequence analysis and quantitative PCR to identify genes which may contribute to agenesis of the corpus callosum.

P-140**ANALYSIS OF QUANTITATIVE TRAIT LOCI THAT INFLUENCE DIVERSITY OF BEHAVIORAL TRAITS BETWEEN C57BL/6 AND MSM/MS**

A Nishi, A Takahashi, T Shiroishi, T Koide

National Institute of Genetics, Mishima, Japan

It is important to choose the appropriate behavior depending on the situation in daily life of animals. A general activity and an emotionality are basic traits related to the survival strategy. It is known that these two traits are regulated by complex genetic mechanisms and exhibit intraspecies and interspecies diversities. In this study, we focused on the behavioral difference between MSM/Ms and C57BL/6, which belongs to *Mus musculus molossinus*, and *Mus musculus domesticus*, respectively. We tried to reveal the quantitative trait loci involved in the difference of general activity and emotionality between these strains. For analyzing the genetic mechanism, we used the consomic strains established from MSM/Ms and C57BL/6. The consomic strains were established by replacing any one chromosome of C57BL/6 with corresponding chromosome of MSM/Ms. First, behavioral traits of consomic strains were compared with parental strains. In the result of the ethological screening, several consomic strains indicated large varieties of general activity and emotionality. In these strains, the traits of C57BL/6.Chr6^{MSM}, which carries chromosome 6 derived from MSM/Ms was dramatically different in the behavior. To map the quantitative trait loci related to the general activity and emotionality on chromosome 6, F2 population made between C57BL/6 and C57BL/6.Chr6^{MSM} were analyzed for the traits. In the result, we obtained two candidate regions. It was revealed that the one associates with emotionality and general activity and the other associates with general activity.

P-141**GENETIC ANALYSIS OF EMOTIONALITY IN B6-MSM CONSONOMIC MOUSE STRAINS**

A Takahashi, A Nishi, T Shiroishi, T Koide
National Institute of Genetics, Mishima, Shizuoka, Japan

Open-field is a commonly used apparatus for assessing genetic contributions to emotionality. We previously reported the great diversity between laboratory strain C57BL/6 (B6) and wild-derived strain MSM on its open-field behavior. To elucidate genetic mechanisms underlying those behavioral differences, we performed further analyses in B6-MSM consomic mouse strains. These strains have the same genetic background as B6 except for one chromosome (x) from MSM (named as B6-xMSM).

More than half of those strains have been analysed so far, and there were many strains that were differed from their parental strain B6. In the open-field ambulation, B6-1MSM, B6-6MSM, B6-11MSM, B6-15MSM, B6-16MSM and B6-17MSM were characterized as hypoactive, while B6-3MSM, and B6-9MSM as hyperactive. By the detailed observation of open-field behaviors, such as stretching, rearing, and grooming, we determined more intimate character of each strain. For example, B6-3MSM was characterized by high frequency of jumping, though both parental strains did not show this behavior often. B6-6MSM and B6-17MSM exhibited high frequency of stretching, which is so-called risk assessment behavior.

Because B6-17MSM had a similar activity at the home-cage as B6 but showed lower activity and higher risk assessment behavior at the novel situation (open-field and elevated-plus maze), we focused on this strain as a high emotional strain. In the fear conditioning paradigm, another test of emotionality, this strain exhibited higher fear response (freezing) to a sound which had previously associated with electrical shock. This again suggested high emotionality in the B6-17MSM. Thus, we are making congenic strains of this strain to identify the genetic factor/factors on Chromosome 17.

P-142**A STUDY OF GENETIC FACTORS RESPONSIBLE FOR DIFFERENCE IN SPONTANEOUS LOCOMOTOR ACTIVITY BETWEEN INBRED STRAINS OF MOUSE**

J Umemori¹, A Nishi^{1,2}, T Shiroishi^{2,3}, T Koide^{1,2}

¹Mouse Genomics Resource Laboratory, National Institute of Genetics, JAPAN. ²Department of Genetics, Sokendai, ³Mammalian Genetics Laboratory, National Institute of Genetics

In the laboratory, mice move spontaneously in the habituated home-cage according to a light/dark rhythm and most mice are active during the dark period. This kind of activity is a basal activity described as spontaneous home-cage activity. In a variety of mice strains, C57BL/6J were relatively hypoactive, in contrast to KJR that were especially hyperactive in the habituated home-cage. In order to detect QTLs responsible for differences in spontaneous home-cage activity between KJR and C57BL/6J, we analyzed F2 progeny (BKF2) that made between C57BL/6J and KJR strains for their total home-cage activity (THA) in three-day measurement. Furthermore, we divided THA into two ethological components, active time (AT) and average activity (AA), and used them for QTL analysis. The QTL analyses identified three significant QTLs, *hyperlocomotive activity related QTL1 (Hylaq1)*, *Hylaq2* and *Hylaq3* associated with THA in a middle region and the telomeric region on chr2, and near the telomeric region on chr10, respectively. Each *Hylaq* locus indicated different effect on AT and AA. Furthermore, QTL analysis suggested that genetic mechanism involved in the spontaneous home-cage activity is different from that of open-field activity which is considered to reflect psychological status of the subject. Finally, we conducted biochemical and pharmacological analyses on the DA systems that consider to be related to the basal activity. The results suggested that the difference in the spontaneous home-cage activity between these strains might be due to the pharmacological difference in downstream pathway of the DA system following activation of the DA receptors.

P-143**A CONGENIC MOUSE STRAIN FOR QTL ON CHROMOSOME 2 AFFECTING GROWTH, FATNESS AND TESTIS SIZE**

A Ishikawa, E Kim, H Bolor, T Tanahashi, H Kodama, T Namikawa
Nagoya University, Nagoya, Japan

Previous QTL studies have identified 24 QTLs for postnatal growth from 3 to 10 weeks of age on 13 mouse chromosomes in an intersubspecific backcross between C57BL/6J and wild *Mus musculus castaneus* with 60% of the body size of C57BL/6J (e.g., Ishikawa et al. Genet. Res. 85:127, 2005). The effect of the most potent QTL (*Pbwtg1*) on proximal chromosome 2 increases linearly with age and accounts for ~12% of the total phenotypic variance. The wild-derived allele at this QTL retards growth. In this study, we succeeded in constructing a congenic strain for the chromosome 2 QTL with an introgressed interval of 44 Mb, by 11 successive backcrossing to C57BL/6J. We compared body weight at 1-10 weeks of age, white fat pads, body lengths and tissue weights between the congenic (n=93) and the C57BL/6J (n=96) strains. The congenic mice showed significantly lower growth from 6 to 10 weeks of age ($0.0004 < P < 0.03$) and had extremely lower fat pad weights and adiposity index ($0.00000001 < P < 0.006$) compared to C57BL/6J. Testis size was also smaller ($0.000001 < P < 0.00001$), but lung, spleen and tail length were slightly greater ($0.02 < P < 0.04$) in the congenic than in C57BL/6J. These results have revealed that the congenic strain constructed clearly has phenotypic effects on growth, fatness and testis size. To narrow down the genomic region(s) underlying these traits, we are now producing an F2 segregating population between the two strains and we are also constructing subcongenics.

P-144**k-CASEIN DEFICIENT MOUSE FAILS TO LACTATE**

P Chandra Shekhar, S Goel, D Selvi Rani, D Partha Sarathi, J L Alex, S Singh, S Kumar
Centre for Cellular and Molecular Biology, Hyderabad (AP), India

Acquisition of milk production capabilities by an ancestor of mammals is at the root of mammalian evolution. Milk casein micelles are a primary source of amino acids and calcium phosphate to neonates. To understand the role of *k*-casein in lactation, we have created and characterized a null mouse strain (*Csnk*^{-/-}) lacking this gene. *Csnk*^{-/-} females failed to lactate due to destabilization of micelles in mammary gland and did not suckle their pups. Thus, *k*-casein is essential for lactation, and consequently for successful completion of the process of reproduction in mammals. In view of extreme structural conservation of casein locus, and phenotype of *Csnk*^{-/-} females, we propose that organization of a functional *k*-casein gene would have been one of the critical events in evolution of mammals. Further, *k*-casein variants are known to affect the industrial properties of milk in dairy animals. Given the expenses and time scale of such experiments in livestock species, it is desirable to model the intended genetic modifications in mouse in the first instance. The mouse strain created by us would be a useful model to the study the effect of *k*-casein variants on the properties of milk and or milk products.

P-145**DETECTION OF QUANTITATIVE TRAIT LOCI AFFECTING SPERMATOGENESIS AND TESTIS WEIGHT FROM THE SMALL TESTIS MUTANT MOUSE**H Bolor¹, N Wakasugi¹, W Zhao², A Ishikawa¹¹ Nagoya University, Nagoya, Japan, ² Henan Agricultural University, Zhengzhou, China

The small testis mutant (Smt) mouse found in the crossbred among C57BL/6 -T/t^{w32}, DDK and CBA/J strains is characterized by the small testis size of 1/3-1/2 the normal. Spermatogenesis in Smt males is arrested at early stages of meiosis. Although a small number of spermatocytes at the late prophase of meiosis, and spermatids can be observed in the mutant testis, spermiogenesis is abnormal. We performed quantitative trait locus (QTL) analysis of spermatogenic traits and testis weight in 221 F₂ males between Smt and MOM (*Mus musculus molossinus*) mice with MapManager QTX. At the genome-wide 5% level, we found nine QTLs affecting meiosis on chromosomes 4, 13 and 7. We also detected two QTLs affecting spermiogenesis on chromosome 1, and six QTLs for paired testis weight as a percentage of body weight on chromosomes 4 and X. In addition, several QTLs for multinuclear giant cells and degenerated cells in the seminiferous tubules of the testis were found on chromosomes 1, 4, 7 and 13. Interestingly, the meiosis QTLs on chromosome 13 was epistatically interacted with the QTLs detected on chromosomes 4, 7 and 8. The chromosome 13 QTL for degenerated cells was also interacted with the chromosome 4 QTL. These results have revealed the polygenic defect of spermatogenesis and testis weight in the Smt mutant. Further genetic studies on the loci identified here will give some insights into understanding the complex mechanisms of spermatogenesis.

P-146**MAPPING OF AUTOSOMAL GENES RESPONSIBLE FOR HYBRID BREAKDOWN CAUSED BY X-CHROMOSOME SUBSTITUTION BETWEEN TWO MOUSE SUBSPECIES**A Oka¹, A Mita¹, R Takahashi², T Aoto², Y Totsuka², M Ueda², N Yamatani¹, H Yamamoto¹, N Takagi³, K Moriwaki⁴, T Shiroishi¹¹ The National Institute of Genetics, Mishima, Japan, ² The YS Institute, Inc., Utsunomiya, Japan,³ Hokusei Gakuen University, Sapporo, Japan, ⁴ RIKEN BioResource Center, Tsukuba, Japan

Reproductive isolation prevents gene flow between genetically diverging populations, and thereby accelerates an accumulation of genetic differentiation and speciation. It is possibly caused by incompatibility between multiple genes of organisms belonging to two diverging populations. Laboratory mouse strain C57BL/6J and Japanese wild mice-derived strain MSM/Ms are genetically differentiated, and are reproductively isolated. F₁ hybrids of the two strains are fertile, but succeeding intercrosses result in male sterility, which should be referred to as hybrid breakdown. We previously reported that a consomic strain, C57BL/6J-X^{MSM}, which carries X-chromosome of MSM/Ms in the C57BL/6J background, shows male sterility, suggesting genetic incompatibility of the MSM/Ms-derived X-chromosome and other C57BL/6J chromosome(s). In this study, genome-wide linkage analysis and subsequent QTL mapping successfully mapped significant QTLs on chromosome 1 and chromosome 11, which are interactive to X-chromosome. Introduction of the QTL regions of MSM/Ms chromosomes into the C57BL/6J with MSM/Ms-derived X-chromosome partially restored fertility. This confirmed that the genetic incompatibility of the relevant chromosomal regions causes hybrid breakdown in C57BL/6J-X^{MSM}. These regions possibly have a crucial role in the reproductive isolation between the two subspecies, *M. m. domesticus* and *M. m. molossinus*, from which C57BL/6J and MSM/Ms strains originated respectively. Furthermore, intra-cytoplasmic sperm injection (ICSI) and zona-free *in vitro* fertilization (IVF) showed that the C57BL/6J-X^{MSM} sperms have a defect only in the penetration of extra-cellular zona pellucida.

P-147**A NETWORK OF CIS- AND TRANS- ACTING GENES AFFECTING PROLIFERATIVE ACTIVITY OF MOUSE HEMATOPOIETIC STEM CELLS (HSC)**

L V Bystrykh, L M Kamminga, R van Os, A Ausema, E Weersing, B Dontje, P Terpstra, R C Jansen, G de Haan
UMCG RUG, Groningen, Netherlands

Previously, we identified two major loci controlling HSC behaviour, namely *Scp2* at ch11 (55-85 Mb) affecting proliferation, and a locus at ch18 (12-32 Mb) affecting HSC pool size.

We have performed genome-wide microarray-based profiling of gene expressions using mRNA isolated from murine hematopoietic stem cells and deposited those data in the www.genenetwork.org database [1]. We have verified the probe sequences against the recent mouse RNA databases and we could find 85% back as perfect matches. With a set of 30 recombinant BXD inbred lines we were able to map controlling loci (QTLs) for thousands of transcripts.

From a list of 12422 probe sets on the Affymetrix Murine Genome U74Av2 GeneChip we identified 3615 transcripts with heritable variation in expression levels. Of these, 399 were highly significantly cis acting (cutoff $-10\log P 2.93$) and 3216 transcripts were trans-acting, whereas only 494 probe sets showed sub-threshold expression levels. We performed quality control and removed false cis acting genes caused by alternative splicing and SNP. From these data we identified candidate genes for HSC controlling loci on ch11 and ch18.

Cis- acting genes are assumed to be primary candidates to cause phenotypic differences as they are expected to carry essential polymorphisms in regulatory regions. Currently we are in the process of verifying this hypothesis using transcription factor and SNP databases.

It is known that serial transplantation of mouse HSC caused gradual deterioration of stem cell function [2]. We performed microarray analysis of serially transplanted HSC, and found 300 genes to be either up- or downregulated. In addition, we have microarrayed HSC isolated from mice in which key stem cell genes were either overexpressed or knocked out, which allowed to identify and verify direct genetic targets of manipulated genes. At present we are in process of constructing a genomic network of candidate genes and their direct targets by integrating genetic information with signaling pathways database, gene ontology database, as well as gene regulation database.

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P-148**DIFFEOMORPHIC NEUROANATOMICAL ANALYSIS USING MRI OF A NEW DOMINANT ALLELE OF *CACNA1A***

J G Sled¹, B J Nieman¹, S J Clapcote², G Xie², R M Henkelman¹, J C Roder²

¹ Hospital for Sick Children, Toronto, ON, Canada, ² Samuel Lunenfeld Research Institute, Toronto, ON, Canada

MRI was used to examine a new ENU mutagenesis derived mutation identified by abnormal gait and termed 'wobbly' from the Centre for Modeling Human Disease in Toronto. Mapping associated this heritable autosomal dominant trait with *Cacna1a*. Whole brain in vivo MRI scans were acquired on a cohort of 8 homozygous mutants, 4 heterozygous mutants, and 5 wildtype controls. Using a 7 Tesla Varian MRI configured for multiple mice, scanning was done in parallel to produce 100 micron resolution 3D datasets. The 3D images were initially aligned to one another by automated linear registration. No significant group differences were observed in overall brain size. Analyzing the homo and heterozygous cohorts separately, deformations were computed using non-linear registration to bring the individual images in each comparison group into exact alignment. The log Jacobian of these transforms, a measure of expansion or contraction, was used to form a student t statistic comparing affected and wildtype groups at each point in the brain. Limiting the false discovery rate (FDR) to 5% of significant voxels, the t statistic map in homozygotes showed significant contraction throughout much of the cerebellum and expansion in part of the forebrain. Using the same significance threshold ($p < 0.004$), a smaller medial region of contraction was seen in the cerebellum of heterozygotes (FDR = 65%). These findings are consistent with cerebellar atrophy affecting Purkinje and Golgi cells previously reported for recessive alleles of *Cacna1a*. The wobbly mutation, however, is consistent with human forms of cerebellar ataxia, which are also dominant.

P-149**PHARMACOGENETICS OF PENTOBARBITAL-MEDIATED SEDATION**

C P D Tu, CC Hsu, B Akgul

¹ IBMS, Academia Sinica, Taipei, Taiwan, ² Pennsylvania State Univ., Univ. Park, PA, United States, ³ Izmir Institute of Technology, Urla, Izmir, Turkey

ENU mutagenesis of mice has become a powerful forward genetic approach to develop and expand the repertoire of novel genes associated with disease phenotypes. We have initiated a genome-wide screen to identify novel gene(s) responsible for sedative response.

Our approach starts with phenotype screening of a library of *N*-ethyl-*N*-nitrosourea (ENU)-mutagenized C57BL/6J (B6) mice for the loss of righting reflex (LRR) following pentobarbital (PB) injection (50 mg/kg, IP), which is then followed by genotyping and gene identification. Our strategy for screening recessive mutants was based on a three-generation mating scheme. Mice that did not show LRR under our assay condition were referred to as having the resistance phenotype.

After screening 639 mice, we have identified from the same pedigree (G1) four mutant G3 mice that lacked LRR under our assay condition. Inheritance test ($n = 483$) with an outcross-intercross scheme indicated that the ENU-induced mutation is inherited in an autosomal recessive manner. Whole genome association mapping with 299 SNP markers localized the ENU mutation to a small region on chromosome 7. Further mapping with more closely spaced SNP markers has apparently narrowed the target to within a ~1.1 Mb region containing less than 30 genes. This region does not contain the $\alpha 1$ or $\alpha 2$ subunits of the GABA_A receptor, which have been mentioned as potential targets for pentobarbital. We will discuss results from the candidate gene approach and expression profile analyses in the context of the GABA_A receptor and of published QTL analysis of pentobarbital-mediated sedation. (Supported by Academia Sinica, Taiwan)

P-150**INTER-SUBSPECIES CHROMOSOME SUBSTITUTION STRAINS OF MICE**S Gregorova, R Storchova, P Divina, P Jansa, K Matejka, M Landikova, B Paigen, J Forejt
Institute of Molecular Genetics AS CR, Prague, Czech Republic

Inter-Species Chromosome Substitution Strains (IS-CSS) of mice represent a powerful tool for dissection of quantitative traits loci (QTLs) affecting development, behavior, reproduction, disease resistance and other biomedically important processes. The parental mouse inbred strains PWD/Ph and C57BL/6J were used as a laboratory representatives of two closely related subspecies of the house mouse – *Mus musculus musculus* and *Mus musculus domesticus*. The last common ancestor of both species lived 350 000 to 1,000,000 years ago, resulting in the accumulation of SNPs and phenotypic differences between them.

On January 2005, fifteen chromosomes of PWD/Ph origin (Nos. 1, 3, 4, 5,6, 9, 12, 14, 15, 16, 17, 18, 19, Y and mitochondrion) have been successfully transferred on the C57BL/6 background and fixed in homozygous (homosomic) state. The remaining seven chromosomes were also transferred, but the reproduction of homosomics was insufficient. These incompatible PWD chromosomes are fragmented into 2-3 segments. An attempt is made to make fertile subchromosomal homosomics by this approach. All fertile homosomic strains are transferred to the Jackson Laboratory, Bar Harbor, Maine, to make them available to the mouse genetic community worldwide. The NIEHS included the PWD/PhJ inbred strain into the set of 15 JAX mouse strains to be re-sequenced by Perlegen Sciences, Inc. The construction of the BAC library from the PWD/PhJ genomic DNA will be also reported

P-151

A STATISTICAL MULTI-PROBE MODEL FOR ANALYZING CIS - AND TRANS-GENES IN GENETICAL GENOMICS EXPERIMENTS WITH SHORT-OLIGONUCLEOTIDE ARRAYS

R Albers, P Terpstra, L V Bystrykh, G de Haan, R C Jansen
Groningen University, Groningen, Netherlands

Short-oligonucleotide arrays typically contain multiple probes per gene. In genetical genomics applications a statistical model for the individual probe signals can help separating `true' differential mRNA expression from `ghost' effects caused by polymorphisms, misdesigned probes and batch effects. It can also help detecting alternative splicing, start or termination. All these effects and artifacts will be discussed.

P-152

MOUSE SNPS IN THE MGI DATABASE: USING LARGE-SCALE GENOMIC VARIATION TO IDENTIFY CANDIDATE GENES FOR COMPLEX TRAITS

C J Bult, S Zhu, B Sinclair, D Qi, D Reed, D Bradt, K Frazer, R Baldarelli, S Cousins, J Winslow, J Beal, J Kadin, J Richardson, L Corbani
The Jackson Laboratory, Bar Harbor, Maine, United States

The laboratory mouse is a powerful experimental platform for identifying the genetic pathways that underlie complex, polygenic diseases affecting humans. The process of identifying probable candidate genes for specific phenotypes can be greatly facilitated by combining data on genome variation among different strains of mice with the biological attributes (e.g., functions, phenotype associations, and expression) of genes. The Mouse Genome Informatics (MGI) database has integrated all publicly available Single Nucleotide Polymorphism (SNP) data for the mouse with the most recent mouse genome annotations to support mining of these data to identify promising candidate genes associated with genetically mapped phenotypes.

Mouse SNP data can be accessed from MGI using several search criteria including strain name, genome coordinates, SNP attributes (variation type, functional class) or by association with specific genes. Query results can be displayed in tabular format or downloaded as a tab delimited text file, which is convenient for saving the data or submitting it to other data analysis software. Mouse SNP data can be visualized graphically using MGI's new interactive sequence feature map called Mouse GBrowse. Mouse GBrowse includes a SNP "track" that shows where specific SNPs are located relative to other genome features and a mouse SNP density plot for each chromosome.

To illustrate the utility of integrating SNP data with gene predictions and functional annotations we used the MGI system to identify candidate genes associated with previously published studies on polycystic kidney disease.

The MGI database is accessible from <http://www.informatics.jax.org>. MGI is supported, in part, by NIH/NHGRI HG00330.

P-153**GENE EXPRESSION DIFFERENCES CORRELATE WITH SPATIAL LEARNING IN MIDDLE AGED MICE ON ATHEROGENIC DIET**

A N Desai, B S Beyer, K P Collins, A F Eisener, T A Gray, B J Herron, G K Kusek, A Messer, R L Pietropaolo, J L Phoenix, M P Ryan, A B Smith, D J Symula, V J Bolivar, L Flaherty

¹ The Genomics Institute, Wadsworth Center, New York State Department of Health, Troy, NY, United States, ² Department of Biomedical Sciences, University at Albany, Albany, NY, United States

Atherogenic diet has been recently linked to the cognitive decline seen in normal aging and progression of Alzheimer's disease. We designed experiments to determine whether an atherogenic diet impairs behavior in C57BL/6 (B6) and 129S1/SvImJ (129S1) mice. Mice were placed on a normal or an atherogenic diet for 21-27 weeks and then subjected to Morris water maze (MWM) paradigm; a measure of spatial learning. Both B6 and 129S1 on atherogenic diet displayed impaired performance on MWM, with the impairment being more pronounced in 129S1. Microarray analyses of hippocampi of these mice revealed altered expression of number of genes including H2-D1, Tgm2 and Ly6 in 129S1 and B6 on atherogenic diet. Moreover, altered expression of these genes correlated with MWM performance of both 129S1 and B6 mice. To determine whether the deficit in MWM performance was evident after 8 weeks on the atherogenic diet, a second set of mice was tested. At this early time no deficits were apparent. After an additional 16 weeks on their respective diets, these same mice were re-tested for MWM performance. During re-testing, even though both strains remembered the MWM experience from the 8 week post-diet test, 129S1 on atherogenic diet failed to improve their ability to find the hidden platform whereas B6 mice improved significantly. Thus, atherogenic diet affected the acquisition of new information but not the retention of previously acquired information. Thus, we have found that the gene-environment interactions affect late onset learning and point to the involvement of specific genes in this process.

P-154**IDENTIFICATION OF A QUANTITATIVE TRAIT LOCUS AFFECTING HIPPOCAMPUS-RELATED BEHAVIOR IN THE INTERLEUKIN-7 RECEPTOR KNOCKOUT MOUSE**

A F Eisener, V J Bolivar, R L Pietropaolo, L Flaherty

The Genomics Institute, Wadsworth Center, New York State Department of Health, Department of Biomedical Sciences, University at Albany, Troy, NY, United States

In an effort to find genes that determine behavioral traits, we have tested a series of knockout/congenic strains for performance in a number of behavioral paradigms. Knockout/congenic strains are derived from 129 embryonic stem (ES) cells that have been genetically engineered to possess a gene ablation and then backcrossed to C57BL/6J (B6) for several generations. Here, we demonstrate that B6-IL7R^{-/-} mice exhibit behavioral deficits in open field and habituation assays as compared to B6 mice. In these studies, we have also considered the possibility that the 129 ES cell-derived genetic regions flanking the ablated *IL-7R* locus may be responsible for the observed trait. Such flanking regions are often retained along with the *IL-7R* locus in the derivation of a knockout/congenic strain. By performing several complementation tests, we have eliminated the possibility that flanking regions are involved and simultaneously determined that the *IL-7R* locus itself affects habituation, generally considered to be a hippocampus-related behavior. Next, we performed microarray analyses of B6-IL7R^{-/-} and B6 strains to determine if these strains differ in hippocampal gene expression. Analyses of these data identified 66 genes which show a significant difference between the two strains ($p < 0.05$ by the Benjamini-Hochberg false discovery rate statistic). We are currently constructing a gene regulatory model to correlate these gene expression results with our behavioral phenotypes.

P-155**CHROMOSOME SUBSTITUTION STRAINS HELP TO DISSECT LARGE QTL INTERVALS FOUND PREVIOUSLY IN F_2 CROSSES, AND REVEAL SIGNIFICANT QTL ON CHROMOSOMES THAT WERE NOT PREVIOUSLY DETECTED**I M Stylianou¹, K Russell², P Magnani¹, B J Paigen¹¹ The Jackson Laboratory, Bar Harbor, Maine, United States, ² University of Missouri-Rolla, Rolla, MO, United States

Increased high-density-lipoprotein (HDL) cholesterol plasma levels are a strong factor in providing protection against cardiovascular disease. Finding the genes controlling HDL levels is therefore of great interest. F_2 crosses using the C57BL/6J (B6) and A/J strains have previously revealed large QTL for HDL cholesterol levels in plasma on chromosomes 1, 8 and 15. However a strain survey of the B6.A/J chromosome substitution strains (consomics) reveals that almost all the consomic strains are significantly different from the parental B6 and A strains. In order to further map the large HDL QTL on chr8 an F_2 intercross was generated using the B6.A/J-Chr8 consomic line. This cross has helped to dissect the large Chr8 interval into several smaller QTL. By using multiple bioinformatics tools such as examining the haplotype distribution of B6 and A/J on Chr8 and the tissue expression profiles of genes in the QTL intervals, several strong candidates have been identified for each smaller QTL. This demonstrates that the consomic strains are a powerful tool for fine mapping larger QTL intervals. A further F_2 cross was performed involving the B6.A/J-Chr3 strain, in which no HDL QTL has been previously found between these strains using the F_2 approach of parental B6 and A/J strains. Our results show two significant QTL, one of which is sex specific. This demonstrates that the consomic strains are a powerful tool for identifying QTL that are not identifiable by performing F_2 crosses with parental inbred strains.

P-156**GENOME-WIDE HAPLOTYPE ASSOCIATION STUDIES TO LOCATE QTL AND QTL GENES**I Stylianou¹, K Russell², P Magnani¹, B Paigen¹¹ The Jackson Laboratory, Bar Harbor, ME, United States, ² University of Missouri-Rola, Rolla, MO, United States

Identifying loci for polygenic quantitative traits (QTL) has traditionally been performed using crosses of inbred lines. With the advent of large SNP genotyping programs for the inbred mouse strains coupled with the Mouse Phenome Project, which measures multiple parameters for each inbred strain, haplotype association studies can detect QTL as well as narrow the QTL detected previously by crosses. We are addressing several statistical and methodological issues to improve the likelihood of identifying true QTL. We apply statistical diagnostic tests to evaluate the histogram of P-value distribution and hence the false discovery rate. Although each trait differs in its pattern, a trait that will yield good QTLs has many more SNPs in the 0-0.01 P-value bin than in bins that have P-values in the non-significant range. This diagnostic histogram of P-values can also be used to measure the impact of various changes; those that improve the chance of detecting true QTL improve the pattern in the histogram. We are evaluating the impact of the size of the SNP-window, the number of strains required, and the type of strains that are the most suitable for this analysis and that are most likely to yield robust results. From our initial analyses we conclude the following. The inclusion of wild derived strains should be avoided because the assumption of haplotype blocks identifying regions that are identical by descent is less likely to be true. Using 30-35 inbred strains is at the lower limit of usefulness depending on the trait. Adding more strains greatly improves the statistics; so far we have added the B6.A consomic strains and we plan to add recombinant inbred strains. Both more SNPs and more strains are desirable, and with the current data (some 18,000 SNPs) a 3-SNP-haplotype block appears to generate the most robust QTL. We have principally used the trait of plasma HDL cholesterol levels in mice as the backbone of the analysis as traditional QTL mapping for this trait is approaching saturation and hence matching computational QTL to those actually found by crosses should provide a guideline of false positive and false negative QTL identification. Between 80-90% of traditional HDL QTL are concordant with the most significant computational QTL. We have applied these rules to several other traits including bone mineral density, blood pressure and red blood cell number.

P-157**GENETIC MODIFIERS OF NPC2 DEFICIENCY IN MICE**

D Symula, K Collins, M Darrah
Wadsworth Center, Albany, NY, United States

Niemann-Pick type C (NPC) disease is a lysosomal storage disorder resulting from defective cholesterol trafficking caused by mutation in the NPC1 or NPC2 genes. One of the hallmarks of NPC disease is the variable presentation for a given mutant allele of NPC1 or NPC2. Childhood forms frequently include hepatomegaly, splenomegaly, and cerebellar neurodegeneration, while adult forms primarily consist of behavioral and cognitive problems. Similarly, mutations in mouse *Npc1* or *Npc2* have different effects on different genetic backgrounds, suggesting that modifier genes mediate the severity or consequences of the trafficking defect. Mice homozygous for a genetrapped mutation in *Npc2*, the BayGenomics LST105 mutation, display phenotypes consistent with human NPC disease and other NPC mouse models, including symptoms of neurodegeneration. Mutants live on average 90 days (range 79 to 119 days) on the inbred 129P2 background but mutants resulting from a 129P2 X FVB/N intercross live an average of 109 days. A difference in male lifespan (92 days on 129P2 vs. 117 days in the F2) accounts for most of this difference. The F2 mutant males fall into three distinct groups based on lifespan, including a group that lives greater than 150 days and shows only mild symptoms of neurodegeneration. Our results suggest that there are a small number of sex-specific modifiers in this cross that have qualitative effects on the neurodegeneration caused by *Npc2* deficiency. We have begun a positional cloning project to identify these genes.

P-158**TESTICULAR GERM CELL TUMOR DEVELOPMENT IN THE 129.MOLF-CHR 19 CONSONIC MOUSE STRAIN**

A Matin, R Zhu, C Bhattacharya
UT MD Anderson Cancer Center, Houston, Texas, United States

We are using the 129 and 129-derived mouse strains to dissect the genetics underlying testicular germ cell tumor (TGCT) development. TGCTs are the most common cancers in young males 15-35 years of age. A polygenic disease model has been suggested for TGCTs in humans but the causative genes have not been identified. The tumors arise from primordial germ cells (PGCs) during fetal development. Very little is understood about how and why germ cells become transformed.

Two mouse strains with high incidence of TGCTs are the 129-*Ter* and the consomic strain, 129.MOLF-Chr 19. To examine how PGCs are affected in the two strains, we introduced the Oct4-GFP (Green Fluorescent Protein driven by the germ cell specific promoter, Oct4) into the *Ter* and CSS strains. Examination of the PGCs in the testes of newborn males show that the mechanism of tumor development differs in the *Ter* compared to the CSS strains. To map TGCT predisposing loci in the CSS, we made congenic strains and identified multiple regions on Chr 19 that predispose to TGCT development. To determine the genes that cause high TGCT frequency in the CSS strain, we examined differences in gene expression in the primordial gonads (embryonic day 13) of the 129 and CSS strains using microarray analysis. A significant number of the differentially expressed genes map to mouse Chr 19 and within the congenic segments. Future work will be directed towards use of transgenic or knockout strategies to assess the contribution of these candidate genes towards tumor predisposition.

P-159**OLIGOGENIZATION OF MULTIGENIC TRAITS: USING A CROSS BETWEEN CONGENIC AND INBRED STRAINS TO REDUCE COMPLEXITY OF QUANTITATIVE TRAITS**

AA Bachmanov, X Li, N Bosak, M L Theodorides, M G Tordoff, G K Beauchamp, D R Reed
Monell Chemical Senses Center, Philadelphia, PA, United States

Positional identification of genes underlying quantitative trait loci (QTL) still remains a challenging task. One of major difficulties of QTL identification is a complex genetic architecture of quantitative traits due to multiple loci segregating in an experimental cross. In this study, we have experimentally tested an approach to simplify the genetic architecture of complex traits. The mouse *Sac* (saccharin preference) locus on chromosome (Chr) 4 corresponds to a sweet taste receptor gene, *Tas1r3*, and pleiotropically affects ingestion of saccharin, sucrose and ethanol in crosses between the C57BL/6ByJ (B6) and 129P3/J (129) strains. In addition to the *Tas1r3* gene, several other QTL polymorphic between the B6 and 129 strains affect these phenotypes. To confirm these other QTL and refine their linkages, we have produced and analyzed an F2 intercross between inbred B6 and congenic 129.B6-*Tas1r3* strain. Elimination of contribution of the *Tas1r3* gene to phenotypical variation in this cross increased phenotypical effects of the other loci and substantially improved their mapping compared with an F2 intercross between the inbred strains, B6 and 129. For example, large increases in significance of linkage were achieved for QTL on Chr 2 (saccharin), Chr 7 (ethanol) and Chr 9 (sucrose). We recommend this approach for reduction of complexity of multigenic traits, which can utilize existing congenic, consomic and recombinant inbred strains.

P-160**MAPPING GENE(S) RELATED TO NOVELTY-INDUCED BEHAVIORS IN INBRED STRAINS OF MICE**

H Shin, S Chae, D Kim, J Lee
Korea Institute of Science and Technology, Seoul, Korea, South

Novelty stimuli cause various behavioral responses such as exploration and avoidance. Human and the rodent share common tendency of conflict between these responses to novelty. We have showed that behavioral responses to novel object were varied among five inbred strains. The BALB/cJ and DBA/2J mice displayed active engagements with novel objects such as gnawing and moving the objects, whereas 129/SvJae showed mild exploratory behaviors. Strain differences in novelty-induced behaviors indicated that such behavioral responses are regulated by genetic factors. In order to identify the gene locus (or loci) associated with novelty-induced behaviors, the breeding scheme of outcross-backcross was applied to the BALB/cJ and DBA/2J with 129Sv/Jae mice. High novelty responder strains, BALB/cJ and DBA/2J mice were separately out-crossed to the low responder strain, 129/SvJae mice. The active manipulations of novel objects were assessed in each of BALB/c*129 F1 and DBA/2*129 F1 mice. BALB/c*129 F1 mice showed the intermediate phenotype of their parents, mild biting (not gnawing). DBA/2*129 F1 mice also exhibited moderate dislocation of the object, and yet had a large variance among individuals. The present results suggest that the phenotypes of novelty-induced behaviors in mice do not follow the simple dominance/recessive pattern, but show the intermediate inheritance. Backcrossing of the hybrid F1 mice with their parental strains is in progress to do linkage analysis for more definite genetic information on novelty-induced behaviors in inbred strains of mice.

P-161**MOUSE KOALA INVERSION MUTATION DISRUPTED NO GENE, BUT EXPRESSION OF *HOXC* GENES WAS ALTERED, AND THE EAR-HAIR UNDERWENT HOMEOTIC TRANSFORMATION**Y You¹, J Sundberg², A Awgulewitsch³, S Mentzer¹, D Carpenter¹, D Johnson¹, E Rinchik¹¹ Oak Ridge National Laboratory, Oak Ridge, TN, United States, ² The Jackson Laboratory, Bar Harbor, ME, United States, ³ Medical University of South Carolina, Charleston, SC., United States

The *Koala* (*Koa*) mutation is associated with a chromosome (chr) 15 inversion. Heterozygous *Koa*⁺ mice display hairy ears and a bushy muzzle. The homozygous *Koa*/*Koa* mice manifest the same phenotype as the heterozygous *Koa*⁺ mice, but they are usually smaller than *Koa*⁺ and its wild-type littermate. We first mapped the *Koa* distal inversion breakpoint using fluorescent *in situ* hybridization with BAC clones on metaphase cell spreads from a *Koa*⁺ mouse and the breakpoint was cloned after Southern blot analyses identified the size-altered inversion-breakpoint-bearing fragment. Consequently, the sequence of the proximal inversion breakpoint was determined based on the sequence of the cloned distal breakpoint. Mapping of the breakpoint sequences to the current mouse genome assembly showed no protein-coding genes were disrupted by the inversion. The proximal breakpoint is located between trichorhinophalangeal syndrome 1 (*Trps1*) and eukaryotic transcriptional-initiation factor 3 subunit 3 (*Eif3s3*), whereas the distal breakpoint is between homeobox c4 (*Hoxc4*) and single-strand selective monofunctional uracil DNA glycosylase (*Smug1*). TaqMan assays for genes that flank the breakpoints revealed that the expression level of *Hoxc* genes was altered in the ears of *Koa* mutants while other genes remained unchanged. *In situ* hybridization of skin sections using *Hoxc4*, *Hoxc9*, and *Hoxc13* as probes confirmed that their expression patterns at the cellular level in the hair follicles did not change. Scanning Electron Microscopy images revealed that the ear-specific hair fibers were changed to pelage-type hair fibers on *Koa* mutant mice. This is the first mouse mutation linking *Hox* gene to skin regional specification.

P-162**IDENTIFYING NOVEL GENES REGULATING ATHEROSCLEROSIS AND PLASMA LIPID CONCENTRATIONS THROUGH MOUSE-HUMAN COMPARATIVE GENETICS**

X Wang, J Rollins, B Paigen

The Jackson Laboratory, Bar Harbor, ME, United States

The genetic determinants of atherosclerosis have been studied by using quantitative trait locus (QTL) analysis. So far, 21 mouse and 27 human atherosclerosis QTLs have been identified. Among the 21 mouse atherosclerosis QTLs, seven were found only in a high fat diet model, nine only in a sensitized model (apolipoprotein E- or LDL receptor-deficient mice), and five in both models, suggesting that different gene sets operate in each model, and that a subset operates in both. Many QTLs for plasma lipid levels have been identified, including QTLs for plasma levels of HDL-C (37 in mice and 30 in humans), LDL-C (25 in mice and 20 in humans) and triglycerides (19 in mice and 30 in humans). We found that most of the identified human QTLs are in homologous regions of the identified mouse QTLs: 63%, 93%, 100% and 80%, respectively, for human atherosclerosis, HDL-C, LDL-C and triglycerides QTLs. This concordance between the two species suggests that many of the atherosclerosis and lipid QTLs in mice and humans have the same underlying genes. Therefore, genes regulating human atherosclerosis and plasma lipid levels will be found most efficiently by first finding their orthologs in concordant mouse QTLs. The following new approaches, based on recently developed genomic and bioinformatic technologies and resources, should greatly facilitate finding these QTL genes: narrowing a QTL by combining crosses, by comparing mouse and human homologous QTLs, by analyzing SNPs and haplotypes, by analyzing *in silico* QTLs, and testing candidate genes by sequence and expression analysis.

P-162**A GRAPH THEORETICAL APPROACH TO SYSTEMS GENETIC ANALYSIS OF GENE TRANSCRIPTION AND COMPLEX PHENOTYPES ACROSS BIOLOGICAL SCALE**E J Chesler¹, J A Scharff², S M Pitts¹, L Lu¹, J Wang¹, K F Manly¹, M A Langston², R W Williams¹¹Center for Genomics & Bioinformatics, University of Tennessee Health Science Center, Memphis, TN, United States, ² Department of Computer Science, University of Tennessee, Knoxville, TN, United States

The construction of molecular reaction networks in complex multi-cellular organisms is challenging because of the diverse spatial and temporal contexts of network activity. Discovering the influences of these contexts across development and through multiple tissues requires an ability to analyze and uncover relationships that transcend time and space. Genetic reference populations are ideal tools for this purpose. Segregated polymorphisms in these populations impact molecular variation in a cascade through development and tissue compartment. Using complex trait analysis in a reference population, we have examined the covariation of phenotypes as a method of defining the architecture of networks and pathways that span across cells and tissues with a focus on the mouse brain.

In our ongoing microarray based genetic analysis of gene transcription in recombinant inbred strains derived from C57BL/6 and DBA/2J (BXD RI) we have identified a small number of chromosomal loci that modulate mRNA abundance of several hundred transcripts each. A major challenge to the construction of networks is the need to extract large sets of co-varying phenotypes from the entire set of post-genomic phenotypic data including high throughput molecular and cellular phenotypes, tissue structure and function, and physiological or behavioral traits. In the present study, we demonstrate the application of graph theoretical approaches to extract sets of molecular phenotypes that share a common genetic regulatory structure and thus contain many members of a common biological network. We further establish the locations of genetic regulators of trait covariance using novel approaches to the genetic analysis of gene transcription and complex higher order phenotypes. Using a combination of genetic correlation analysis, multiple QTL models and clique-based algorithms, we have identified loci that modulate the expression of mRNA at the synapse, including components of the synaptic vesicle cycling system. A single locus has been identified which regulates the abundance of well over 1500 transcripts. A system of 10 loci accounts for as much as 55% of the trait variance for each of 1278 transcripts. The relationship of the cliques of genetically correlated transcript abundances to systems level phenotypes such as pre-pulse inhibition, taste preference, and many others demonstrates the utility of this mouse reference population for biological research across all levels of scale.

P-164**THE ORIGINS AND USES OF MOUSE OUTBRED STOCKS**R Chia¹, F Achilli¹, M F W Festing², E M C Fisher¹¹Department of Neurodegenerative Disease, Institute of Neurology, London, UK; ²c/o MRC Toxicology Unit, Hodgkin Building, University of Leicester, Leicester, UK

Outbred stocks of mice and rats are often used in fundamental biomedical research as well as in applied disciplines such as toxicology and pharmacology. However, when isogenic strains are available, such use is often inappropriate. Increased phenotypic variability leads to low powered experiments or the need to increase sample sizes, the genotype of individuals is unknown, and it is not possible to repeat experiments using genetically identical animals. Outbred stocks are also subject to genetic drift as a result of inbreeding and directional selection. However, outbred stocks have been used extensively as base populations for selective breeding to develop new animal models and recently, because of their low levels of linkage disequilibrium, researchers from the field of complex trait analysis have used them to refine the identification of quantitative trait loci. We stress the importance of understanding the characteristics of these stocks, and of generating useful results without wasting animal lives and resources on suboptimal experiments. Here, we present the first attempt to list the most widely used outbred stocks of mice, their origin and selection in experimental designs.

See page 29 for P-165